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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,491	11/30/2001	Radmila Mileusnic	3578-120	6361

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EXAMINER	
SEHARASEYON, JEGATHEESAN	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,491	MILEUSNIC ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *12-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/02 & 12/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner J. Seharaseyon of Art Unit 1647.

2. Applicant's election without traverse of Group I, drawn to a peptide in filed 12/19/2003 is acknowledged. Claims 12-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the response filed 12/19/2003.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

4. The disclosure is objected to because of the following informalities: On page: 20, lines 28-29 of the specification Applicant has identified an oligonucleotide sequence as SEQ ID NO: 9. However, claims 10 and 11 have a polypeptide sequence with the SEQ ID NO: 9. In addition, the sequence listing refers to the polypeptide sequence as SEQ ID NO: 9. Thus, appropriate correction is required in the specification to reflect the correct SEQ ID NO: number.

5.The Office acknowledges the receipt of declaration filed under 37 C.F.R 1.132 dated 7/16/02 to clarify the authorship.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7a. Claim 1 is rejected as being vague and indefinite in the recitation of the terms "sequences closely homologous" or "nonstandard amino acids or derivatives of amino acids". It is not clear what Applicant considers to be the closely homologous sequences. In addition, Applicant has not indicated the various nonstandard and derivative amino acids contemplated, which can be part of the sequence. Furthermore, claim recites "sequences in which said amino acids thereof are replaced by nonstandard amino acids and/or by derivatives of said amino acids" but fails to indicate the upper limit of the substitution. Accordingly, the metes and bounds of the claim cannot be determined.

7b. Claim 1 is indefinite in that they only recite the polypeptide of interest by an arbitrary name human APP. There is nothing in the claims that distinctly identifies the polypeptide. For example, others in the field may isolate and use the same protein, giving the said protein an entirely different name. Applicants should particularly point out and distinctly claim the "APP" polypeptide by sufficient identifying characteristics associated with the protein (e.g. amino acid sequence, molecular weight, etc.). Claiming biochemical molecules by a particular name given to the polypeptide by various workers in the field fails to distinctly claim what that protein is.

7c. Claims 8, 9 and 11 are rejected as being indefinite in that it is not clear if the "further" molecule cause the transport or merely not impede the transport of the polypeptide across the blood-brain barrier.

The remaining claims are rejected for depending from an indefinite claim.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8a. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification discloses various amino acid sequences on pages 2 and 3. The specification specifically describes the polypeptides corresponding to SEQ ID Nos: 3-11(pages 2-3). This meets the written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose all possible sequences including those that are closely homologous to the reverse order sequence of human APP 332-328 or sequences in which said amino acids thereof are replaced by nonstandard amino acids and derivatives of said amino acids. The claims as written, however, encompass polypeptide sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph

because the written description is not commensurate in scope with the recitation of claims 1-8. Specifically, although the specification provides for written support for SEQ ID Nos: 3-11 it does not describe the other contemplated peptide sequences with nonstandard amino acids and derivatives of amino acids. The specification does not provide written description to support the genus encompassed by the instant claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116).

With the exception of peptide sequences corresponding to SEQ ID Nos: 3-11, the skilled artisan cannot envision all the detailed chemical structure of the claimed polypeptide sequences regardless of the complexity or simplicity of the method of identifying the sequences. Applicant has failed to set forth any defining characteristics of the agents or molecules. No common structural or functional features essential for the claimed function are described, nor are a representative number of members of the claimed genus of polypeptides are presented.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only the of peptide sequences corresponding to SEQ ID Nos: 3-11, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the

genus because the genus is highly variant. As a result, it does not appear that the inventors were in possession of various polypeptide sequences set forth in claims 1-8.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

8b. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for of peptide sequences corresponding to SEQ ID Nos: 3-11, does not reasonably provide enablement for the scope of all possible polypeptide sequences contemplated by the Applicant. In addition, while enabling for direct injection into the brain it is not enabled for the peripheral administration to cross the blood brain barrier. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the

invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Claims 1-11 recite "sequences including those that are closely homologous to the reverse order sequence of human APP 332-328 or sequences in which said amino acids thereof are replaced by nonstandard amino acids and derivatives of said amino acids". The specification only describes, that RERMS and RER sequences prevent the β-amyloid 12-28 induced short-term memory loss in the chicken model (pages 19-23). In addition, published art suggest that peptide sequences RERMS, SMRER and RER to be involved in memory rescue (Applicants own work, Mileusnic et al. (2000), Reference: AE on 1449 of June 11 2002). Furthermore, there is published art that contradicts Applicants observation in that it states that the reversed sequence (SMRER) and RER do not possess growth-promoting activity (see pages 11 and 18, Saitoh et al. (1994), Reference: AB on 1449 of June 11 2002). Thus, the instant specification is only enabling for amino acid sequences RERMS, SMRER, RSAER and RER and not commensurate with possible sequences claimed by the Applicant. In addition, Applicant fails to provide or teach activity limitations for the claimed polypeptide other than the prevention of the short-term memory loss attributed to the polypeptides. Furthermore, the specification has taught how to make and use amino acid sequences RERMS, SMRER, RSAER and RER and not the breadth of claims because it fails to describe the

breadth of the sequences to be used in the β-amyloid 12-28 induced short-term memory loss in the chicken model.

Therefore in the instant application, the level of unpredictability of the art is great as demonstrated by Saitoh et al. (1994). The lack of working examples and the quantity of experimentation needed to determine the limitless number of peptide sequences including those that are closely homologous to the reverse order sequence of human APP 332-328 or sequences in which, said amino acids thereof are replaced by nonstandard amino acids and derivatives of said amino acids, is practically infinite and the guidance provided in the specification is very limited (For example, no activity limitation is provided). Absent further guidance from the specification it would constitute undue experimentation to determine all the possible sequences including those that are closely homologous to the reverse order sequence of human APP 332-328 or sequences in which said amino acids thereof are replaced by nonstandard amino acids and derivatives of said amino acids. Absent further guidance from the specification it would constitute undue experimentation to determine all the claimed polypeptides contemplated by the Applicant. As such, claims 1-11 is not commensurate in scope with the specification but rather is broader than the supporting disclosure.

Furthermore, claims 8, 9 and 11 recites, "... whereby the polypeptide can be delivered across the blood-brain barrier". The specification describes the delivery of the peptides intracerebrally into chicks to evaluate the effects on memory (page 20). In addition, published art also teaches the direct injection of peptide sequences RERMS, SMRER and RER into the brain of chicks to be involved memory rescue (Applicants

own work, Mileusnic et al. (2000), Reference: AE on 1449 of June 11 2002). Saitoh et al. (1994) have also injected RERMS, AKERLEAKHRERMSQVM and MVQSMRERHKAELREKA in saline into the rat brain. Applicant has not demonstrated how and with what compound the peptides of interest can be conjugated or linked for the purpose of administering peripherally to cross the blood brain barrier. Thus, the instant specification is only enabling for delivering these peptides by direct injection into animal and not enabled for administering peripherally to cross the blood-brain barrier (page 18). In the instant application, the quantity of experimentation needed to determine the limitless number of compounds and the various methods for conjugation or linking the peptides to cross the blood brain barrier, is practically infinite and the guidance provided in the specification is very limited. Absent further guidance from the specification it would constitute undue experimentation to determine all the possible compounds and the methods of conjugating or linking a vehicle for delivering claimed polypeptide peripherally to cross the blood brain barrier. As such, claims 8, 9, 11 are not commensurate in scope with the specification but rather are broader than the supporting disclosure.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7 and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Saitoh et al. (1994, WO 94/09808).

The instant invention describes the pharmaceutical compositions comprising RER polypeptide and the delivery of the polypeptide across the blood-brain barrier.

Saitoh et al. (1994), describe several polypeptide sequences including RERMS, RER, AKERLEAKHRERMSQVM and MVQSMRERHKAELREKA (see pages 17 and 18). The reference also teaches the injection of these polypeptides in saline solution (pharmaceutical composition) directly into the rat brain thus, delivering polypeptide across the blood brain barrier (page 48-54). Therefore, claims 7 and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Saitoh et al. (1994, WO 94/09808).

10. No claims are allowable.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Mileusnic et al (2000) Eur. J. of Neurosci.. 12, pages 4487-4495. (Reference: AE on 1449 of June 11 2002). Mileusnic et al discloses the delivery of peptides to chick brain to study memory formation. The declaration filed on 7/16/02 under 37 CFR 1.132 is sufficient to overcome the Mileusnic et al. reference.

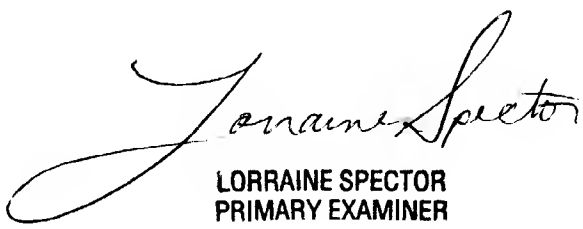
Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS



LORRAINE SPECTOR
PRIMARY EXAMINER